

SYNTHESIS OF POLYCYCLIC NITROGEN-CONTAINING HETEROCYCLES: ONE POT FORMATION OF 1,6-NAPHTHYRIDINE RING SYSTEM BY REACTION OF AMINO-CYANO-METHYLTHIO-HETEROCYCLES WITH DIALKYL ACETYLENEDICARBOXYLATES

Yoshinori Tominaga* and Noriko Yoshioka

Faculty of Pharmaceutical Sciences, Nagasaki University, 1-14, Bunkyo-machi, Nagasaki 852, Japan

Abstract-----The reaction of 5-amino-6-cyano-1,3-dimethyl-7-methylthiopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**1c**) with dimethyl acetylenedicarboxylate (DMAD) in the presence of potassium carbonate in dimethyl sulfoxide gave tetramethyl 8,9,10,11-tetrahydro-8,10-dimethyl-9,10-dioxo-4*H*-pyrimido[4',5':5,6]pyrido[2,3,4-*cb*][1,6]naphthyridine-2,3,5,6-tetracarboxylate (**2c**). The reaction of other heterocycles bearing amino, cyano, and methylthio groups with DMAD or DEAD under the same reaction conditions gave the corresponding tetracyclic heterocycles containing the fundamental 1,6-naphthyridine ring system.

In connection with our program of preparing new polyheterocyclic compounds which are of interest from both theoretical and practical standpoints and which might also exhibit potential biological activity, we have recently described the synthesis of some pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine and 1*H*-1,4,7-triazaphenalene derivatives.¹ These polycyclic heterocycles are readily prepared by the key reaction of *o*-aminonitriles² or ketene *S,N*-acetals,³ which are highly reactive starting materials, with dimethyl acetylenedicarboxylate (DMAD) in the presence of a base. Hexamethyl 1*H*-1,4,7-triazaphenalene-2,3,5,6,8,9-hexacarboxylate is also readily prepared by the double addition-cyclization reaction of 3-amino-3-methylthio-2-cyano-acrylonitrile with excess DMAD in the presence of potassium carbonate in dimethyl sulfoxide (DMSO).⁴ This method can be conveniently applied to the synthesis of 1,6-naphthyridine containing polycyclic heterocycles. We now wish to report the reaction of various pyridine or pyrimidine derivatives bearing amino, cyano, and methylthio groups with dialkyl acetylenedicarboxylates in the presence of a base such as

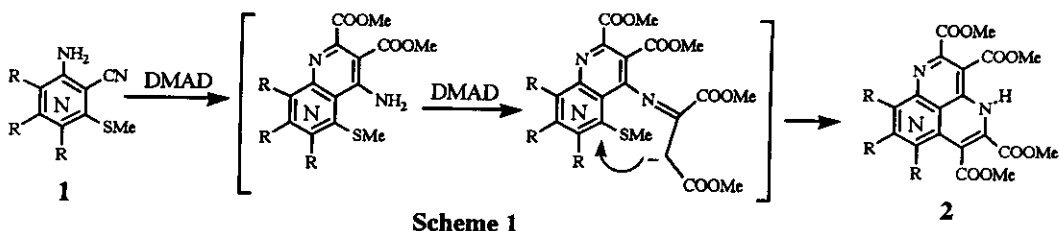
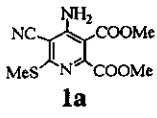
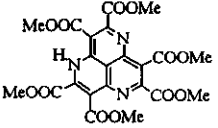
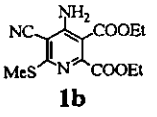
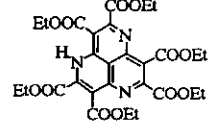
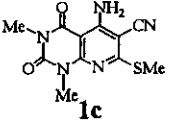
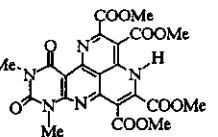
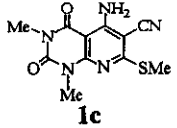
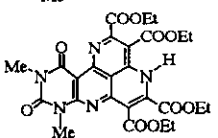
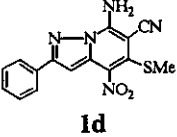
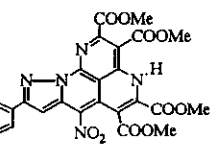
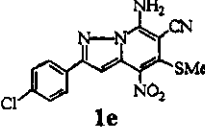
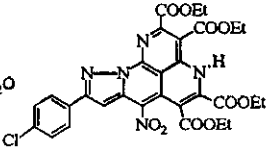
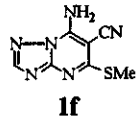
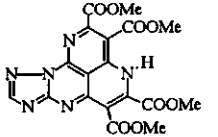
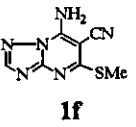
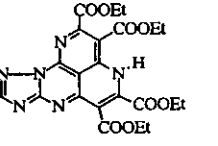
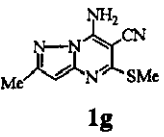
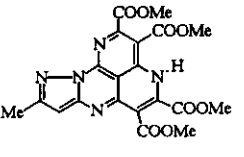


Table 1. Reaction of Amino-cyano-methylthio-heterocycles with Dialkyl Acetylenedicarboxylates in the Presence of Base^a

Entry	Aminonitrile	Acetylenic comp.	Base	Product	Yield(%)
1	 <p>1a</p>	DMAD	K ₂ CO ₃ K ₃ PO ₄ ·H ₂ O	 <p>2a³</p>	68 70
2	 <p>1b</p>	DEAD	K ₂ CO ₃	 <p>2b</p>	63
3	 <p>1c</p>	DMAD	K ₂ CO ₃ K ₃ PO ₄ ·H ₂ O	 <p>2c</p>	53 35
4	 <p>1c</p>	DEAD	K ₂ CO ₃	 <p>2d</p>	59
5	 <p>1d</p>	DMAD	K ₂ CO ₃	 <p>2e</p>	75
6	 <p>1e</p>	DEAD	K ₃ PO ₄ ·H ₂ O	 <p>2f</p>	56
7	 <p>1f</p>	DMAD	K ₂ CO ₃	 <p>2g</p>	43
8	 <p>1f</p>	DEAD	K ₂ CO ₃	 <p>2h</p>	23
9	 <p>1g</p>	DMAD	K ₂ CO ₃	 <p>2i</p>	47

a) The reactions were carried out in a system of **1** (20 mmol), DMAD or DEAD (30 mmol), and K₂CO₃ or K₃PO₄·H₂O (50 mmol) at room temperature in DMSO.

potassium carbonate to obtain the polycyclic nitrogen-containing tri- or tetracyclic heterocycles by one pot formation of the 1,6-naphthyridine ring system, as shown in Scheme 1.

A system of amino-cyano-methylthio-heterocycles containing pyridine or pyrimidine rings is an important and versatile synthetic starting material for construction of fused pyridine or pyrimidine derivatives. These heterocycles are generally obtained by the reaction of ketene dithioacetals³ with various nucleophiles.

The reaction of **1a** with DMAD in the presence of potassium carbonate as a base in DMSO gave an expected tricyclic heterocycle, hexamethyl 1*H*-1,4,7-triazaphenalene-2,3,5,6,8,9-hexacarboxylate (**2a**) in 68% yield.⁴ Tripotassium phosphate hydrate could also be employed as a base in this reaction, giving a yield of 70%. Diethyl acetylenedicarboxylate (DEAD) also reacted with **1b** under a same reaction condition to give **2b**⁵ in 63% yield. In a similar manner, the reaction of 5-amino-6-cyanopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**1c**),⁶ which was prepared by the condensation of 6-aminouracils with ketene dithioacetal, bis(methylthio)methylenepropanedinitrile, with DMAD in the presence of potassium carbonate or tripotassium phosphate gave tetracyclic heterocycle (**2c**)⁷ in 53 and 35 % yields, respectively. As shown in Entry 4, the reaction of **1c** with DEAD was also carried out under the same reaction conditions to give the corresponding tetra cyclic compound (**2d**)⁸ in 59% yield. The corresponding pyrazolopyridine derivatives (**1d**, **1e**)⁹ were allowed to react with DMAD giving the corresponding tetracyclic compounds (**2e**)¹⁰ and (**2f**)¹¹ in 75 and 56% yields, respectively.

The above reaction could be readily applied to synthesis of fused pyrimido[4,5,6-*d,e*]-[1,6]naphthyridine derivatives (**2g-h**),^{12,13} which were prepared by reaction of the corresponding triazolo[1,5-*a*]pyrimidine derivative (**1f**) with DMAD or DEAD in the presence of potassium carbonate. Similarly, reaction of pyrazolo[1,5-*a*]pyrimidine derivative (**1g**) with DMAD was carried out to give the corresponding tetracyclic compound (**2i**)¹⁴ in 47% yield.

A typical experimental procedure is as follows: To a stirred mixture of 2.77 g (10 mmol) of **1c**, 6.9 g (50 mmol) of anhydrous potassium carbonate and 30 ml of dimethyl sulfoxide, a solution of 4.2 g (30 mmol) of dimethyl acetylenedicarboxylate in 5 ml of dimethyl sulfoxide was added dropwise over 10 min at room temperature. Stirring was continued for an additional 48 h at room temperature. The reaction mixture was poured into 300 ml of ice-water, acidified with 10% hydrochloric acid, and stirred for 30 min. The precipitate was collected by filtration. After drying in air, the product was recrystallized from methanol to give 2.72 g (53%) of yellow needles (**2c**), mp 290-293°C.

In conclusion, the tandem addition-cyclization reaction of amino-cyano-methylthio-pyridine or pyrimidine derivatives with dialkyl acetylenedicarboxylates in the presence of appropriate base was found to be a versatile method of forming polycyclic heterocycles containing the 1,6-naphthyridine ring system.

REFERENCES AND NOTES

- 1 a) Y. Tominaga, J. -K. Luo, L. W. Castle, and R. N. Castle, *J. Heterocycl. Chem.*, 1993, **30**, 267; b) Y. Tominaga, R. N. Castle, and N. K. Dalley, *J. Heterocycl. Chem.*, 1993, **30**, 295; c) H. Matsunaga, M. Sonoda, Y. Tomioka,

- and M. Yamazaki, *Chem. Pharm. Bull.*, 1986, **34**, 396; d) H. Matsunaga, M. Sonoda, Y. Tomioka, and M. Yamazaki, *Chem. Pharm. Bull.*, 1984, **32**, 2596 .
2. a) E. C. Taylor and A. McKillop, *Advances in Organic Chemistry*, Vol. 7; "The Chemistry of Cyclic Enaminonitrile and α -Aminonitrile", ed. by E. C. Taylor, Interscience; New York, 1970; b) J. M. Robinson, L. W. Brent, C. Chau, K. A. Floyd, S. L. Gillham, T. L. McMahan, D. J. Magda, T. J. Motycka, M. J. Pack, A. L. Roberts, L. A. Seally, S. L. Simpson, R. R. Smith, and K. N. Zalesny, *J. Org. Chem.*, 1992, **57**, 7352 .
 3. a) A. Kumar, H. Ila, and H. Junjappa, *J. Chem. Soc., Perkin Trans I*, 1978, 858; b) M. Yokoyama and K. Sato, *Synthesis*, 1988, 813; c) R. T. Chakrasali, H. Ila, and H. Junjappa, *Synthesis*, 1988, 87; d) D. Pooranchand, H. Ila, and H. Junjappa, *Synthesis*, 1987, 547; e) F. -C, Ye, B. -C. Chen, and X. Huang, *Synthesis*, 1989, 317; f) A. Hosomi, Y. Miyashiro, R. Yoshida, Y. Tominaga, T. Yanagi, and M. Hojo, *J. Org. Chem.*; 1990, **55**, 5308; g) R. C. Anand and A. K. Sinha, *J. Chem. Soc., Perkin . Trans. I*, 1991, 2339, h) Y. Tominaga and Y. Matsuda, *J. Heterocycl. Chem.*, 1985, **22**, 937; i) Y. Tominaga and Y. Matsuda, *J. Synth. Org. Chem. Japan*, 1985, **43**, 669; j) R. K. Dieter, *Tetrahedron*, 1986, **42**, 3029; k) Y. Tominaga, *J. Synth. Org. Chem. Japan*, 1989, **47**, 413; l) Y. Tominaga, S. Kohra, H. Honkawa, and A. Hosomi, *Heterocycles*, 1989, **29**, 1409; m) M. Kolbe, *Synthesis*, 1990, 171; n) H. Junjappa, H. Ila, and C. V. Asokan, *Tetrahedron*, 1990, **46**, 5423; o) Y. Tominaga, *Trends in Heterocyclic Chemistry*, 1991, **2**, 43; p) R. Gompper and W. Topfl, *Chem. Ber.*, 1962, **95**, 2861.
 4. Y. Tominaga and K. Nomoto, *Heterocycles*, 1994, **37**, 235
 5. **2b**: mp 154°C, yellow needles. $^1\text{H-nmr}(\text{CDCl}_3)$: 1.15-1.56 (18H, m, 6xOCH₂-CH₃), 4.31-4.56 (12H, m, 6xOCH₂-CH₃), 12.43 (1H, br s, NH), FAB ms 602(M⁺+1).
 6. Y. Tominaga, S. Kohra, H. Okuda, A. Ushirogouchi, Y. Matsuda, and G Kobayashi, *Chem. Pharm. Bull.*, 1984, **32**, 122.
 7. **2c**: mp 290-293°C, yellow needles. FAB ms 514(M⁺+1).
 8. **2d**: mp 225-231°C, yellow needles. Ms 569(M⁺, 4), 496(3), 425(5), 354(5), 277(5), 44(100).
 9. Compounds (**1d**) and (**1e**) were produced by reaction of 5-nitromethyl-3-phenylpyrazoles with bis(methylthio)-methylenepropanedinitrile in the presence of potassium carbonate in DMSO in 87 and 91% yields, respectively. Similarly, compounds (**1f**) and (**1g**) were also prepared by reaction of the corresponding 3-aminotriazole and 3-methyl-5-aminopyrazole with bis(methylthio)methylenepropanedinitrile.
 10. **2e**: mp 282-287°C, orange needles. Ms: m/z 561(M⁺, 3), 529(100), 515(36), 498(41), 483(57), 419(26), 413(54).
 11. **2f**: mp 270°C(decomp.). orange needles. Mas: m/z 653(M+,3), 652(6), 651(M+,7), 632(19), 620(50), 45(100).
 12. **2g**: mp 217-219°C, yellow leaflets. Ms: m/z 443(M⁺+1, 4), 442(M⁺, 16), 411(4), 384(18), 321(8), 268(7), 45(100).
 13. **2h**: mp 197-199°C, yellow needles. Ms: m/z 499(M⁺+1, 9), 498(M⁺, 30), 354(21), 353(14), 282(24), 45(100).
 14. **2i**: mp 245-247°C, yellow needles. Ms: m/z 456(M⁺+1, 18), 455(M⁺, 73), 423(100), 307(32), 279(21), 45(12).
 15. An N-H group in **2a** and **2b** is clearly shown in ir and nmr spectra, while N-H group in compounds (**2c-2i**) are not fixed by any particular nitrogen atom. In the present paper, we are drawing by tentative assignment of configuration to the N-H group in Table 1.

Received, 30th January, 1995